Sudden Unexplained Death in Epilepsy

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Sudden unexplained death in epilepsy (SUDEP) accounts for 7–17% of deaths among people with epilepsy. Both cardiac and pulmonary derangement have been postulated as proximate causes. Patients with uncontrolled seizures are at greatest risk for SUDEP, and experiencing tonic-clonic seizures, taking multiple antiepileptic drugs and having coexisting neurologic disease further increase the risk.

Mortality rates are considerably higher in people with epilepsy than would be expected in a healthy population. Sudden unexplained death (SUDEP) in epilepsy is often listed as a cause of death, accounting for 7–17% of deaths among the general population with epilepsy and perhaps 50% among patients with refractory epilepsy. (1–8) This puzzling term concisely encapsulates our lack of understanding, although not knowledge, about an important cause for excess mortality in epilepsy. This article briefly reviews what is known about SUDEP.

Criteria have been suggested by a variety of investigators to diagnose SUDEP (9,10). A reasonable synthesis would yield the following requirements:

1. The victim must have had epilepsy, defined as recurrent unprovoked seizures.
2. Death must have occurred unexpectedly, with no obvious medical cause, while in a reasonable state of health, in the absence of trauma or drowning.
3. Death must have occurred suddenly when observed.
4. There may or may not have been evidence of a seizure, but status epilepticus must not have occurred. Evidence for a seizure could consist of either a witnessed seizure or clinical evidence such as a bitten tongue or cheek.

An autopsy that does not reveal a cause for death is required for the diagnosis of definite SUDEP, whereas a diagnosis of probable SUDEP is given to those who fit the previously mentioned criteria without autopsy. Possible SUDEP would include cases in which SUDEP seems a reasonable diagnosis, but there is insufficient evidence regarding the circumstances of death and no autopsy is available.

The reported incidence of SUDEP spans a wide range, from 0.35 deaths per 1000 person-years in a population based cohort (1) to 6 deaths per 1000 person-years in a cohort with refractory epilepsy (7). In a population based study, the risk of sudden unexplained death was 24 times higher than that seen in the general population (1). Although much effort has been devoted to defining the incidence of SUDEP, there is an inherent variability in risk which relates to the nature of underlying population. The general population includes the elderly and the young, and the medically ill and the otherwise healthy; consequently the proportion of deaths from SUDEP and the SUDEP mortality rate is lower. On the other hand, cohorts chosen from epilepsy clinics or epilepsy surgery series represent the other end of the patient spectrum. These consist of otherwise healthy, relatively young individuals who have fewer other reasons to die; hence, SUDEP achieves a greater prominence as a cause of death. The underlying characteristics of epilepsy differ among the different populations as well, and as will be discussed below, this also influences the incidence of SUDEP.

Knowing the risk of SUDEP has become important because it may potentially influence whether a new drug or device is approved for marketing in the U.S. by the Food and Drug Administration (FDA). SUDEP rates have been carefully studied before or after regulatory approval (2,3,9,11), with burdens placed upon companies to demonstrate that there is no increased mortality rate associated with their product. While there is some value in defining the incidence of SUDEP, sweeping generalizations about incidence rates do not seem justified because the risk seems dependent upon individual characteristics. What characteristics are shared by patients at highest risk for SUDEP? Early studies suggested that male gender, cerebral lesions, developmental delay, a history of ongoing tonic-clonic seizures, and subtherapeutic anticonvulsant levels predominated in patients who died of SUDEP (12,13).

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Subsequent work has yielded some conflicting data, yet certain features seem to predominate in most SUDEP series (7,8,14–17). The bulk of evidence supports the concept that patients with uncontrolled seizures are at greatest risk for SUDEP, and that patients with well controlled epilepsy, that is, no seizures, are not at increased risk. There is also a suggestion that seizure frequency may be related to risk of SUDEP, as patients with frequent seizures die more often than those with few seizures. None-the-less, it is abundantly clear that even patients with rare seizures, experiencing as few as 1 per year, are at increased risk of dying. Seizure type also influences risk. Tonic-clonic seizures convey the greatest risk of SUDEP, though sudden death can occur in the absence of tonic-clonic seizures (e.g., in patients with complex partial seizures) (1,7,8,10,16).

The relationship between SUDEP and seizures has been further elucidated in a recent study (10). SUDEP was witnessed in fifteen patients, presumably by non-medical personnel who were later interviewed. Twelve of the fifteen had a witnessed tonic-clonic seizure in association with SUDEP, and two more were in a post-ictal state at the time of death. In 12 cases, witnesses observed difficulty breathing. Resuscitation was performed in 13 of the 15 cases without success, immediately by family or staff in eight cases. SUDEP is also a phenomenon that seems to occur in the patient's domicile; two thirds of 135 patients in the series by Langan et al. (10) died while in bed, and most of the remainder died elsewhere in the home.

Concomitant neurologic illness may also influence SUDEP risk. While structural lesions were not found to be associated with SUDEP in some recent series, mental retardation, which is a marker of brain dysfunction, appears to be significant risk factor in a recent analysis (8). The mechanism underlying this remains to be elucidated, but it is consonant with the known high standardized mortality rates in retarded populations.

Anticonvulsant medication may also relate to risk of SUDEP. Initially, low medication levels were noted in autopsied cases (13), and it was suggested that poor compliance led to seizures and subsequent death. Recent studies cast doubt on this explanation. Opeskin et al. (18) found no evidence for poor medication compliance or lower levels in patients who died of SUDEP than in case controls. While Nilsson et al. (15) related less frequent therapeutic drug monitoring to a higher risk, SUDEP was not associated with low serum drug levels. However, two recent studies (8,15) note an association between polytherapy and SUDEP. Patients on multiple drugs appeared to have a higher SUDEP rate. Whether this reflects a risk conveyed by antiepileptic drugs or rather the presence of more severe epilepsy remains uncertain, though some efforts were made to account for differences in seizure frequency in both series. One report (15) noted an association between high carbamazepine levels and SUDEP; this finding should be viewed with caution, and it requires replication.

The mechanisms of death in SUDEP remain unknown, with both cardiac and pulmonary derangements having been hypothesized (19–22). There is evidence supporting cardiac arrhythmias as the terminal event. Ictal EKG studies and autopsy studies find evidence for transient ictal conduction abnormalities and myocardial injury, respectively. There are several reports documenting terminal arrhythmia or bradycardia in patients who died on monitoring units. Central apnea has also been hypothesized to produce SUDEP. There is one case report of post-ictal apnea leading to cardiac arrest, (20) and status epilepticus in sheep was associated with death from hypoventilation (23). Since both cardiac and pulmonary mechanisms can account for SUDEP, it is likely that etiology is patient and seizure dependent.

While all death is tragic, SUDEP seems especially heartbreaking since it tends to strike young, otherwise healthy individuals. Progress will be made only as risk factors are defined and mechanisms of death elucidated. Once this happens, appropriate preventative measures can be taken to minimize this complication of uncontrolled epilepsy. Until then, physicians should strive to completely control seizures, since even infrequent seizures pose risk of death.

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